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6/23/01

Dear Dr. Dow

In preparation for our upcoming meeting at Vical, I have reviewed the various patents at issue (US#5264618 and US#5459127), as well as what I believe to be all relevant documents in my possession.

These documents fall into two categories;

1) **Documents, memoranda, agreements, other legal documents, and research notes from my time at Vical as well as the documents associated with my activities prior to Vical employment. These documents were obtained from two sources, documents that I was permitted to retain in anticipation of manuscript preparation as well as records provided to me by Vical employees after my departure.**

2) **The research, disclosures, communication and patents developed at the Salk Institute. Of these, I have only a partial record, as the file wrappers from the Salk are being mailed to me but have yet to be received. I have also spoken with Dr. Verma concerning his recollection of those days. Not yet in my possession is documentation of the original conception of genetic vaccination using retroviral vectors, but this will be obtained as it was a filed patent application.**

You had requested that I prepare a summary of relevant documents for your review prior to our meeting, and that I forward this summary so that it arrives in advance.

I have organized the information into documents relevant to the above patents (US#5264618 and US#5459127), and a second group of documents relevant to the original discovery of direct polynucleotide delivery (what many refer to as "naked DNA").

Concerning patents US#5264618 and US#5459127, I assert that I was one of the key inventors of the technologies and composition of matter described in the patents.

Some of these inventive contributions occurred prior to my employment at Vical, and others occurred in the context of that employment.

I am prepared to file a petition to have the inventorship corrected and to undertake the process of having these supporting documents examined by the court.

In support of these assertions, I bring the following to your attention:

In both patents US#5264618 and US#5459127, a substantial fraction of the data included in the application was obtained by my own hands, in the course of experiments that I designed, implemented and interpreted. There are also multiple claims in these patents to which I directly contributed, and claims in US#5459127 that were directly disclosed as inventions by myself either while at the Salk or at Vical.

Summary and context of documents concerning both US#5264618 and US#5459127

Project planning and responsibility documents

1) Initial gene delivery program budget composed by RMalone prior to starting lipid development project
2) Project outline developed after hiring Virginia Lee (mid 1989) when project was well under way
3) 5/31/89 meeting summaries RE: Vical/WARF. Note explicit acknowledgment of pre-existing Salk technology derived from Verma lab. Martha to create technology map.
4) Technology map. Note explicit recognition of Salk position in RNA and nucleic acid vaccines.
5) 6/16/89 Summary of progress and task list for RMalone from PFelgner. Note RMalone role in developing, formulating, screening compounds and formulations, RMalone primary role in blinded Wolff studies.
6) Resignation letter specifically documenting that the work was a continuation of ongoing Salk work. For the record, the in vivo work was specifically what I had proposed to Walter Eckhart (Salk) for my PhD thesis studies.

Relevant invention disclosures and patent documents

1) 1/11/88 Disclosure from Salk concerning RNA as a drug, stabilization of RNA for this purpose, and in vivo delivery with lipids. These ideas were shared with PFelgner while he was an employee at Syntex in the context of my ongoing collaboration with him.
2) "Docket 48014" page from patent filed from the Salk Institute covering prior work.
3) Letter from UC OTT concerning DNA embryo transfection work involving cationic lipid formulations for in vivo use
4) 2/2/89 disclosure by RMalone concerning stabilized RNA

5) **3/7/89 disclosure of core concepts that predates discovery of direct polynucleotide delivery.**
6) **6/1/89 Vical invention disclosure prepared and submitted by RMalone but inappropriately countersigned by PFelgner as a co-inventor. RMalone disputed this act by Felgner to Karl Hostetler (then scientific VP), who instructed PFelgner to cease from such actions. Note direct relevance to claims 25 – 33 of US 5,459,127**
7) **Early draft manuscripts, published abstracts, protocols etc. Note abstract entitled "A novel approach to study..." published in 1988. Note also first Vical published abstract on polynucleotide delivery.**

RMalone data and figures specifically correlating to figures and data in the above patents for which RMalone is not a named inventor.

Self explanatory. Example from patent on top of each packet followed by specific RMalone data including experimental design from which the patent information was derived

General data, figures, and experimental design directly relevant to above patents from Rmalone lab notes.

Note the extensive documentation of the toxicity of the lipid/polynucleotide complexes. Was this disclosed to the FDA?

<u>Documents relevant to the original discovery of direct polynucleotide delivery and DNA Vaccines patents (what many refer to as "naked DNA").</u>

I suggest that at issue here is;

1) The preceding work and inventions concerning RNA and DNA delivery and gene therapy-based vaccines at the Salk/Verma Lab by RMalone. The initial development of the concept of gene therapy-based nucleic acid vaccination, the concept of mRNA and transient gene therapy (including RNA as a drug), initial formulation testing and use of DNA and mRNA with cationic lipids in vivo-including formulation development and testing. Routine use of negative controls of free DNA, free RNA and lipid alone for in vivo work were performed by RMalone while at the Salk prior to employment at Vical. This is why the discovery occurred so rapidly. Jon Wolff had no prior experience with mRNA or cationic lipids prior to initiating the collaboration. PFelgner had never worked with <u>any</u> *in vivo* systems for gene delivery and had no training or experience in immunology or molecular biology prior to this time. In contrast, RMalone had been working with animal models, virology, molecular biology, gene transfer studies (in one of the leading laboratories) including lipid studies, and had received training in immunology both in medical school and as a graduate student at UCSD.

2) The actual events resulting in the discovery, and the roles played by each of the three initial inventors (Malone, Felgner, Wolff). These events have been often misrepresented in public lectures (see letter to Jon Wolff 6/25/97), published manuscripts (for example, Felgner, Scientific American RE: DNA Vaccines), and personal communication by Jon Wolff and Phil Felgner. The actual experimental record should be corrected once and for all based on documents, not the biased recollections and spin of Jon and Phil.

3) The continuing assertions by Jon Wolff of his principal role in that he "Discovered the ability of naked DNA to be taken up by muscle and more recently, liver cells" and by Felgner of his conception of "DNA Vaccines", both of which are incorrect.

4) Actions of Felgner and Wolff damaging to RMalone (see #3 above- additional examples are readily provided) both while they (PF, JW) were at Vical or associated with Vical and continuing subsequently after no longer being associated with the firm.

5) Vical apparently misrepresented that they approached or were going to approach Dr. Verma to obtain a license to RMalone inventions (under Salk/UCSD agreements, Dr. Malone would have collected revenue from such as agreement). Although Verma was an employee/consultant for Vical at and around the time when he decided to drop the potentially interfering Salk patents (without notification or consultation to inventors Malone or StLouis), he claims (phone call on 6/22/01) to have no recollection of any discussions with Vical or its representatives concerning relevant Salk intellectual property. Therefore, when RMalone assigned rights to "Naked DNA", "Cationic lipid/polynucleotide vaccine" and "DNA vaccine" patents (Divisionals and continuations US #5,580,859, #5,589,466, #5,703,055, #6,214,804) he was misled to believe that those aspects covered under the Salk applications were excluded. Instead, Vical claimed such inventive contributions made at the Salk as Vical intellectual property, but provided no compensation to RMalone for same.

In retrospect, Dr. Verma's assertions that he "didn't recall" is almost a direct admission that he was involved in having the Vical patent applications dropped. Note Verma did not say that he didn't do it.

Exhibit A: Salk Institute Data-

The enclosed manuscripts "Cationic liposome-mediated RNA transfection" and "mRNA transfection of cultured cells and embryos using cationic liposomes" document much of the Salk data concerning RNA (including an example of the use of the typical "negative control" of polynucleotide without cationic lipid, but do not document the full extent of the embryo work. This embryo work was the subject of a patent filed from the Salk but dropped by Verma at or about the time that he served as a paid Vical advisor.

Preceding these manuscripts, please find multiple examples of the use of such controls in 1988 for in vivo transfection work carried out exclusively by RMalone at the Salk prior to Vical employment. Please note that this work from Salk was

disclosed and discussed on multiple occasions at Vical, that PFelgner was aware of these studies and findings prior to his employment at Vical, and that the optimized formulations developed at the Salk for in vivo use were those initially used by Wolff based on extensive telephone advice and consultation by RMalone.

Exhibit B: VICAL documents preceding RMalone employment-

Experimental plan prepared by Jon Wolff and Phil Felgner without knowledge of RMalone. Note the specific description of the experimental groups and lack of controls of "naked DNA" or "lipids alone". Also note that there is no mention of anything even remotely resembling the idea of gene therapy-based vaccination. Nor were there any plans concerning mRNA.

At the same time and prior to the preparation of this proposal by Felgner and Wolff, RMalone was routinely using these controls in his experiments involving in vivo transfection including formulation testing (see exhibit A), and was working closely with Dr. Dan StLouis in association with the discovery to immune responses to a retrovirally-encoded transgene.

Note also that these studies were actually performed using NIH funding (NIH-funded rats- as I recall from a core facility), and yet NIH was not informed of the discovery (against the law, by the way) and the records were amended by agreement between the University of Wisconsin and Vical post-facto to hide this fact so that the PHS would have no claim on the discovery.

Exhibit C: Experimental data from Vical in vivo delivery project

Note: To provide continuity, four sets of documents have been integrated:
-One set is my actual lab notes.
-The second is a letter sent to Phil in which Jon first reports the results of the experiments where he has included the controls that I recommended to him as he had performed the first experiment without controls.
-The third is a retrospective set of documents that Jon prepared long after the experiments were actually performed, although he writes the summary as if it were the actual experimental record. Note that in every case in the retrospective summary where issues of the RNA alone control is mentioned he seems to write as if he was the one that was insisting that the RNA control be done. However, a careful read of the data summarized as "FIRST RNA EXPERIMENT" etc. clearly demonstrates that it was written as a retrospective summary. Even the naming of the pages points this out. Notice also that there is no interpretation of the last experiment "RNA CAT 7". This was the experiment that resulted in a halt to the studies and a request that he summarize results to date. Beginning after the first experiment in which the negative control was positive and he explained this as being due to mis-loading of the TLC plate, I had begun sending him blinded samples. When he sent back the data on what he indicates is the seventh experiment the result indicated that samples with lipid alone were the most strongly and consistently positive. However, the "free RNA" was also positive. At this point I became very wary of both Jon and Phil and increasingly cautious

about the whole collaboration. My concerns triggered a pause in the studies, a re-consideration of the collaboration and structure of Vical interactions with Wolff, and a request that he summarize findings to date and send them to Vical. When they were resumed (with the blinded samples of 6/5/89, I believe) they initially continued as blinded controls but then Phil took me off of that project and put me full time on the lipid optimization, Nef antisense etc. projects and Phil and Jon continued with the studies.

-The fourth set of documents are the only copies of the actual lab book record that I have from Jon's lab. Note that the lab book record starts immediately after the second RNA experiment was performed- the one that was the first to include the negative control. Has Vical ever seen the pages from that book that precede 2/13/89? Also note that the growth hormone studies continued on in this lab book record for quite a while without there being any "Naked DNA" control included in those studies, further reinforcing that I was the only one that took the "SECOND RNA EXPERIMENT Lane 11" data seriously for quite a while, and that I was the one pushing for more experiments with "Naked RNA". It was only in retrospect that Jon recognized the importance.

Based on these data summarized in this section, I assert that Jon not only did not "discover" direct transfection with free polynucleotide, he does not meet inventorship criteria as I understand them to be defined.

1) 1/24/89 Wolff summary of "FIRST RNA CAT EXPERIMENT". Note that it is only in this retrospective summary that Jon indicates the need for the negative controls, but he writes it as if it was his idea.

   This was the first observation that a lipid/RNA formulation resulted in transfection of muscle. Note that I was advising Jon on how to do the formulations and experiments via phone. When I discussed the initial result with the chemist that had synthesized the lipid (Dr. Raj Kumar) he objected that he did not believe the data and that we were not doing good studies. In response to Raj's objections, I called Jon and recommended that the next experiment include the negative controls that I had often performed previously- lipid alone and mRNA alone. But Jon writes as if this was his idea.

2) Letter from Jon Wolff to Phil Felgner including first experiment with the negative control of mRNA alone.

   This letter was the first data provided back from Jon after that experiment. Note that although Jon includes an interpretation of the experiment in this initial letter to Phil, but he does not indicate any interpretation of lane 11- "RNA by itself". I called Jon about this data and noted that lane 11 was positive. Jon indicated that he believed that the lab worker must have mis-loaded the lane. However, in the retrospective summary of this experiment titled "CAT RNA 2 experiments" he appears to indicate that he initially correctly interpreted the experiment. Funny that he only mentions this in the retrospective!

3) 2/2/89 "RNA CAT 3" Rather than focusing on the RNA only control, which in his retrospective summary he indicates that he correctly interpreted as

indicating that the RNA was transfecting without added lipid, he sets up his own experiment and focuses on RNA/lipid and lipid only. Nothing works.

4) 2/9/89 "RNA/CAT 4" Things do not work well at all. RNA alone does not work at all, but it is clear from the pure CAT protein lane that he is not doing the assay well, so my interpretation is that the data is inconclusive.
5) "CAT RNA 5" At this point I have begun sending him blinded samples. When we break the code, the pure RNA is most consistently active.
6) 3/2/89 "RNA CAT 6" Jon runs his own experiment with archived mRNA that I had sent him previously. Results indicate that mRNA alone works.
7) 3/16/89 "RNA CAT 7" I have again prepared blinded samples and done so in a fashion that makes it hard for him to determine which blinded group is which. See attached information from my own lab notes on this experiment. The data comes back, I break the code, and the strongest positive results are with lipid without any added CAT mRNA or DNA. At this point I alert Vical management that there is something wrong here, and that we cannot trust Jon.
8) Jon Wolff lab book notes spanning 2/13 to 2/17 in which there are NO DNA alone of lipid alone controls.

Exhibit D: Relevant Vical documents involving RMalone employment and invention activities

Exhibit E: Documentation of inappropriate Wolff invention claims.

1) Recent CV of Jon Wolff asserting his discoveries of naked DNA delivery to muscle and liver. Jon submitted this abbreviated CV to the ASGT in support of his candidacy for election to the board of directors of the society.
2) Notice of disclosure to Bob Zaugg of RMalone findings with direct hepatic delivery as well as use of "Bioject" apparatus for muscle delivery. Note that RMalone published and disclosed to Vical "Naked DNA" delivery to liver at a time when Vical and Wolff claimed that the phenomenon was restricted to muscle tissue. Soon after receiving the letter, Dr. Zaugg called me and threatened legal action.
3) Letter from RMalone following J Wolff presentation in 1997

Exhibit F: Current RMalone CV.

Note that, at the time RMalone published direct DNA delivery to liver (1992 discovery and abstract presentation, publication in 1994), Jon Wolff and Phil Felgner had spent years working on liver delivery and had concluded that "Naked DNA" only worked in muscle. If Jon and Phil were so committed to the appropriate ("Naked DNA") controls as they assert, why did they not discover this? Why does Jon Wolff now claim to have discovered naked DNA delivery to liver? Why was RMalone able to

1) complete medical school,
2) complete an internship, and then
3) discover direct gene delivery to liver,
4) develop and patent multiple novel cationic lipids and lipid formulations (now forming core IP for Genteric),